

Skin Necrosis Associated With Warfarin Sodium

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BLEEDING DUE TO THE suppression of vitamin K-dependent clotting factors is a familiar complication of oral anticoagulant drugs. Cutaneous reactions of various types have been reported,¹⁻³ but a more serious complication is necrosis of skin and subcutaneous tissue. This complication is widely reported in European literature—more than 150 cases in 50 reports—but rarely in the American literature.⁴ Although seven coumarin derivatives and phenidione have been implicated, bishydroxycoumarin, ethyl biscoumate and phenprocoumon are the most common offenders. Coumadin® (warfarin sodium) has been previously implicated in only six cases.⁴⁻⁸ This article describes the clinical and pathological findings in two additional cases of skin necrosis associated with warfarin sodium therapy.

Reports of Cases

Case 1.—A 30-year-old Caucasian man with a previously diagnosed adenocarcinoma of the lung was admitted to Tripler General Hospital because of sudden onset of pleuritic pain in the left side of the chest.

On admission he was noted to be debilitated, apparently chronically ill and in acute respiratory distress. Respirations were 28 per minute. On physical examination, splinting and tenderness were noted on the left side of the chest, with rales and dullness to percussion at the left base. There was a positive cuff test on the left and tenderness over the left thigh with 2+ pitting edema of the left leg and ankle.

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Initial laboratory data were normal except for hemoglobin of 9.9 gm per 100 ml of blood. Coagulation studies showed adequate platelets on peripheral smear, normal prothrombin time and fibrindex, and partial thromboplastin time of 116 seconds (control 82 seconds). An x-ray film of the chest showed bilateral pleural effusions. A lung scan, using Risa I¹³¹, was consistent with a diagnosis of pulmonary embolism to the left lower lobe.

Heparin was given intravenously, 75 mg every six hours. On the third hospital day heparin was discontinued because of hemoptysis, and then was reinstituted on the seventh hospital day. From the tenth to the twelfth hospital day, in addition to heparin, the patient received warfarin sodium by mouth in daily doses of 25 mg, 15 mg, and 10 mg, respectively. Prothrombin time increased from 13 seconds to 22 seconds (control 13 seconds). Forty-eight hours after the first dose of warfarin, the patient complained of severe, persistent bilateral mid-thigh pain. Within eight hours large, ecchymotic, well demarcated areas of superficial necrosis developed on the inner aspect of both thighs. Because hemorrhage due to excessive anticoagulation was suspected, all anticoagulants were discontinued. The patient's condition steadily deteriorated and he died on the twenty-second hospital day.

Necropsy showed widely disseminated, undifferentiated carcinoma with the primary lesion in the right upper lobe bronchus, multiple pulmonary emboli with infarction of the left lower lobe, thrombophlebitis of the left external iliac and femoral veins, nonbacterial vegetative endocarditis of the mitral valve, and occlusion of the right middle cerebral and left coronary arteries by atherosclerotic processes.

Case 2.—A 50-year-old Caucasian man was admitted to Tripler General Hospital for evaluation of migratory thrombophlebitis. Three weeks before admission, while he was in Vietnam, dysuria and pain and swelling of the penis developed. Prostatitis was diagnosed and he was treated with gantrisin by mouth. The drug was discontinued after four days when development of tender subcutaneous nodules raised suspicion of allergic sensitivity to it. Five days later, intravenous heparin therapy was started because of development of superficial and deep thrombophlebitis in the veins of the left hand, both calves and the dorsal vein of the penis. At that time

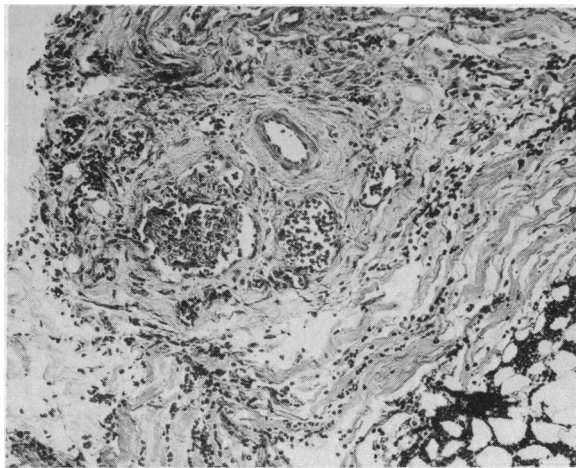


Figure 1.—Section of subcutaneous tissue taken at postmortem examination of Patient 1, demonstrating interstitial edema and mural edema of the vein and partial venous thrombi. There is some extravasation of red blood cells. Note the artery is relatively uninvolved and there is no inflammatory exudate. (Hematoxylin and eosin stain, X75)

the patient was transferred to Tripler General Hospital.

Physical examination showed resolving thrombophlebitis of the dorsal veins of the left hand and dorsal vein of the penis. The left foot and leg were slightly swollen and tender, without pitting edema. A cuff test was negative and there was no tenderness over the saphenous vein. The toes of the right foot were mottled and cyanotic, but peripheral pulses were present.

Initial laboratory data were within normal limits. Coagulation studies showed normal Lee-White clotting time, prothrombin time, partial thromboplastin time, fibrinogen, and quantitative platelet count.

Intravenous heparin therapy was continued, 7500 units every six hours, and oral warfarin therapy was started. Over the next four days the patient received doses of 50 mg, 15 mg, 10 mg, and 12.5 mg, respectively. Prothrombin time by the fourth day was 30 seconds (control 12 seconds) and partial thromboplastin time was 86 seconds (control 32 seconds). On the second day, the middle toes of the right foot showed bluish-black discoloration with well demarcated, erythematous edges. On the fifth hospital day he complained of excruciating pain in the left thigh and there was associated mottling and erythema of the skin. All anticoagulants were discontinued because hemorrhage was suspected. On the eighth hospital day a large circumferential

area of bluish-black discoloration developed on the left thigh. It had a well demarcated, erythematous border which surrounded a large bulla containing sanguineous fluid. Further coagulation studies failed to document an intravascular coagulation syndrome. Despite complications of transient renal failure and a gastrointestinal hemorrhage, the patient's condition improved over the next three weeks. Surgical debridements, skin grafts of the left thigh, and amputation of the gangrenous toes of the right foot were required over the next several weeks. The patient left the hospital fully ambulatory, with minimal muscular and neurological deficits.

Pathology of Cutaneous Lesions

Skin and subcutaneous tissues were obtained at necropsy on Patient 1, and at various intervals on Patient 2 over a two-week period. Similar changes were noted in both cases, but with varying degrees of involvement. In the apparent early stage the epidermis appeared uninvolved, and the dermis showed only edema and vascular congestion. In the subcutaneous tissue there was prominent edema and vascular engorgement with extravasation of red blood cells. Small areas of fresh hemorrhage were seen. The veins showed mural edema and endothelial proliferation. Endothelial nuclei were swollen, and early thrombosis of the veins was seen. The arteries and small vessels appeared uninvolved (Figure 1). No significant inflammatory change involving either the vessels or surrounding tissues was seen.

Comment

In both cases the syndrome of skin necrosis secondary to oral anticoagulants, as described in the literature,⁴⁻¹⁶ was demonstrated. Within three to ten days after oral anticoagulant therapy is begun, the patient complains of superficial, excruciating pain in an area with abundant subcutaneous fat, such as the abdomen, thigh, buttock or breast. The involved skin is erythematous and petechial. There is a rapid progression to a homogeneous blue-black discoloration, clearly demarcated by a border of erythema. Within 24 hours, bulla formation and frank necrosis are evident. The necrotic area sloughs, leaving a large tissue defect which generally requires debridement and skin grafting.

In cases where early histologic examination of the lesions is reported, the changes are quite similar to those noted in the two cases here reported. Vascular edema and endothelial proliferation with thrombosis of the venules, rather than hemorrhage, are prominent; and the vascular involvement is almost exclusively limited to veins, venules and capillaries, sparing arteries and arterioles. Perivascular leukocyte infiltration, perivascular hemorrhage, and nuclear pyknosis have also been described. Eosinophilic infiltration and foreign body giant cells have not been reported.

The management of patients with suspected skin necrosis secondary to oral anticoagulants is symptomatic and usually dictated by the underlying illness. Continuation or cessation of anticoagulant therapy does not seem to affect the natural progression of the lesion. Subsequent re-administration may or may not cause recurrence of new lesions. It may be advisable, therefore, to substitute heparin sodium (which to our knowledge has never been implicated in skin necrosis) when anticoagulation is still required. Vitamin K, steroids and vasoactive drugs do not affect the course or prognosis. Symptomatic management for control of pain with debridement and, sometimes, plastic surgical procedures are the treatments of choice.

The pathogenesis of this unique entity is poorly understood. The depletion of coagulation factors might contribute to the extent of the hemorrhage, but would not logically produce localized thrombosis and necrosis. An argument against depletion of coagulation factors being etiologically involved is that most patients are within therapeutic range of anticoagulation. An allergic or toxic vasculitis in sensitive persons has been proposed,¹⁴⁻¹⁶ but subsequent administration of the drug or skin testing with the drug has failed to elicit an allergic reaction.^{9,10,17} Hormonal mechanisms^{5,18} and a hypercoagulable state^{6,14} have been proposed but not substantiated. McCarter et al¹⁴ have suggested that skin necrosis secondary to oral anticoagulants may represent a form of localized Schwartzman reaction. However, experimentally induced localized Schwartzman reactions show a prominent polymorphonuclear infiltrate¹⁹ and such an inflammatory exudate is notably absent in most of the reported cases. This would cast doubt upon the validity of this hypothesis.

It is unlikely that the orally administered anticoagulants can act as either the preparatory or the provoking substance for the localized necrosis attributed to their use. It is more likely that underlying disease processes, including intravascular coagulation, sepsis, or localized inflammation, trigger a localized purpuric reaction which then is intensified by the coumarin therapy. One can only speculate that continuous heparin therapy would either prevent the reaction or perhaps limit the degree of involvement, as has been suggested in previous reports.^{6,9}

Summary

In two patients, one a 30-year-old man with disseminated lung cancer and multiple pulmonary emboli and the other a 50-year-old man with migratory thrombophlebitis, necrosis of the subcutaneous tissue of the thighs and legs developed three to five days after therapy with Coumadin (warfarin sodium). Biopsy of tissue demonstrated venous thrombosis and interstitial hemorrhage, but no evidence of allergic vasculitis.

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